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Revitalising the drug pipeline:

AntibioticDB, an open access database to aid antibacterial research and development

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Synopsis

The current state of antibiotic discovery, research and development is insufficient to respond to the need for new treatments for drug-resistant bacterial infections. The process has changed over the last decade with most new agents in phases 1-3, or recently approved, having been discovered in small and medium-sized enterprises (companies; SMEs) or academia. These have then been licensed or sold to large companies for development with the end goal of taking them to market. However, early drug discovery and development, including the possibility of developing previously discontinued agents would benefit from a database of antibacterial compounds, to be scrutinised by the developer. This article describes the first free, open-access searchable database of antibacterial compounds, including discontinued agents, drugs under pre-clinical development and those in clinical trials: AntibioticDB (**AntibioticDB.com**). Data were obtained from publicly available sources. This article summarises the compounds and drugs in AntibioticDB including their drug class, mode of action, development status and propensity to select drug-resistant bacteria. AntibioticDB includes compounds currently in pre-clinical development and 834 that have been discontinued and that reached varying stages of development. These may serve as starting points for future research and development.

Introduction

In 2009, the WHO declared antibiotic resistance one of the biggest threats to mankind.[1] One answer to the crisis seems simple: to generate new antibiotics. However, it takes approximately 10-15 years from the discovery of a compound, to progress through pre-clinical and clinical development before a medicine can be licensed and then marketed.[2] Furthermore, the average expenditure required to research and develop a compound is estimated at ~$350 million[3] (not including failures which can increase the cost to ~$5 billion)[4]. This cost could bankrupt a small or mid-size company. Once an antibiotic has been discovered, data must be provided to show a safety profile suitable for human testing. This pre-clinical development phase typically provides animal pharmacokinetic data, toxicity profiles and efficacy against the bacterial target.

Before compounds can be tested in human clinical trials, an institution must apply to the appropriate national or regional drug regulatory authority indicating that, based upon pre-clinical data, the drug is deemed safe to be tested in humans. In the USA, an Investigational New Drug (IND) application from the United States FDA must be granted before testing can commence. A similar process exists for the EU via the EMA, and in Japan and China. Typically, 17.3% of antimicrobial compounds in pre-clinical development proceed to phase 1 clinical trials.[2] Once an IND application has been granted, pre-marketing clinical trials are split into three phases (Table 1).

There is no doubt that the antibiotic pipeline needs revitalisation; however, the answer may not only be the development of new drugs, but also re-investigating compounds previously discontinued. Unfortunately, no database exists that collectively records the discovery of compounds and those in pre-clinical and clinical development with those that did not become approved drugs, or the reasons for the lack of development or approval. There is an existing database of microbial compounds, but this only provides chemical and physical data on some drugs.[5]

This article describes the first publicly accessible free database of antibacterial compounds, AntibioticDB. This includes links to data on discovery, research and clinical trials, those awaiting approval from the FDA/EMA and discontinued compounds. AntibioticDB aims to serve as a platform for future research, antibiotic discovery and development.

Methods

Sources of antibacterial compounds

Compounds and drugs were identified by reading material from numerous sources including from (1) the ASM Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC) or European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) conferences from 1961 to 2016; (2) Journal of Antimicrobial Chemotherapy, Antimicrobial Agents and Chemotherapy, Journal of Medicinal Chemistry, and Bioorganic and Medicinal Chemistry Letters; (3) Google patent searches (https://patents.google.com) with the search terms 'antibiotic' and 'antibacterial'. Additional names of compounds and drugs were obtained by discussion with key opinion leaders who had worked in the Pharmaceutical industry. Once names had been obtained, information on each compound/drug was obtained by additional internet searches e.g. on PubMed.

Where available, links to published abstracts are included in AntibioticDB. For abstracts before 2013, the year the compound was first described is indicated. Wherever possible, any compound described in pharmaceutical or biotech company literature or website and/or by research institutes and/or universities has also been included. If a compound has been developed by an organisation with a website that details the current status of the compound, this website is listed. If a compound has been patented, the web address is indicated regardless of whether the patent has expired or not. Information regarding drug patents was primarily obtained by Google's patent search feature. Drugs in clinical trials included in AntibioticDB were not limited to those only under FDA or EMA approval, but also included outside drug monitoring organisations such as, but not limited to, the Pharmaceuticals and Medical Devices Agency, Japan (PMDA). Table 2 shows the definitions of terms used in AntibioticDB. Bracketed compounds in AntibioticDB represent the most promising compounds of a series of analogues. Information on the inferior derivative compounds can often be found in the reference provided.

Limitations of AntibioticDB

The current focus of AntibioticDB is compounds active against Gram-positive and/or negative bacteria; compounds that target *Mycobacterium tuberculosis* are not currently included. It is intended that AntibioticDB will be continually updated and extended. Individuals and organisations

are invited to contribute information subject to peer review by BSAC. AntibioticDB has a short web-based form to facilitate this process.

In contrast to the abstracts presented after 1990, in the earlier years of ICAAC, very few of the presented abstracts were uploaded in full to the internet, meaning that available data on some of the compounds is very scarce. In this case, AntibioticDB serves as a platform for interested parties to contact original authors to obtain information directly that cannot be found elsewhere in the literature.

Results

AntibioticDB, comprises two types of data. Firstly, antibacterial compounds in current development and for which data has been published since April 2013. This information is indicative of the current antibiotic development pipeline. Secondly, compounds described between 1961 and 31st March 2017 that were discontinued at varying stages of development. There are 147 pre-clinical compounds listed currently under research and/or development; 77 have some activity against Gram-negative bacteria. Only six of these compounds state they specifically target MDR Gram-negative infections; examples include NAB-739, a polymyxin derivative (Northern Antibiotics) and FSI-1686 a carbapenem (Merck & Co.). Some companies have focused on creating analogues of pre-existing compounds with a better pharmacology profile than predecessor compounds of the same class. As a result, some novel compounds are being developed that belong to pre-existing drug classes. Kibdelomycin, a type II topoisomerase inhibitor (Merck & Co), targets *C. difficile* infections and has a low propensity to select resistant bacteria.[6] Nabriva Therapeutics has an on-going pre-clinical programme investigating extended spectrum pleuromutilins (ESPs), specifically aimed at Gram-negative bacteria.[7]

Data from AntibioticDB demonstrates that as of 31 March 2017, there were 53 compounds in active research and development: 12 in phase 1, 20 in phase 2, 19 in phase 3, and 2 in pre-registration. A few compounds in clinical trials are claimed to display novelty in their field with unique modes of action that currently display no modes of resistance. For instance, brilacidin is a member of a new class modelled on host defence proteins (HDP-mimetics); (defensin mimetics). Two antimicrobial peptides are in clinical trials: LTX-109 (Lytixar™, Lytix Biopharma) and Pexiganan™ (Dipexium Pharmaceuticals); both are topical agents for Gram-positive infections. Radezolid (Melinta Therapeutics, USA) is an oxazolidone currently in phase 2 that has shown successful results against uncomplicated skin and skin-structure infections (uSSS) and community-acquired pneumonia (CAP). There are currently 834 discontinued compounds in AntibioticDB, some of which are available to purchase for research.

Compounds in AntibioticDB

Aminoglycosides (20 in AntibioticDB)

Aminoglycosides are broad-spectrum agents derived from Streptomycetes natural products and contain amino sugar subgroups. Their act via inhibition of protein synthesis through binding to the ribosomal 30S subunit. There are currently two listed in AntibioticDB currently in research and development, one in pre-clinical and one in phase 3 trials. FY-901, currently in pre-clinical development by Changzhou Fangyuan Pharmaceutical, China, is being developed to treat MRSA. Achaogen, USA, has developed plazomicin (ACHN-490) an aminoglycoside with Gram-negative activity including multidrug-resistant Enterobacteriaceae. Following results from two phase 3 studies, EPIC (urinary tract infections (UTIs)) and CARE (bacteraemia), Achaogen expect to submit a New Drug Application in the USA and a Marketing Authorization Application (MAA) in Europe during 2017/8.[8] The development of 18 aminoglycosides was discontinued, many due to intolerable levels of toxicity. One example is TS2037 (Meiji Seika Pharma., Japan), a derivative of arbekacin, which showed good *in vitro* broad-spectrum activity, but was discontinued because of its high levels of nephrotoxicity.

Anthracyclines (Three in AntibioticDB)

Anthracycline IT-62-B was reported by Taisho Pharmaceuticals (Japan) as having Gram-positive activity. Consistent with the current use of anthracyclines as anti-tumour chemotherapeutics,[9] this molecule was discontinued as an antibacterial due to its cytotoxicity in humans.

Antibodies (Eleven in AntibioticDB)

Antibodies are immune effector molecules that identify and begin the cascade leading to eradication of foreign material (including bacteria). This is achieved by opsonisation of the target bacteria by cells of the immune system. Attenuation of pathogenic bacteria can be by directly blocking a bacterial component essential to virulence (e.g. adhesins or toxins) through binding of specific monoclonal antibodies. These differ from the mechanisms of action of typical antibiotics, suggesting that cross resistance is unlikely, making monoclonal antibody therapy an attractive option for treatment of bacterial disease.[10] An example of an indirectly neutralising antibody in

AntibioticDB is Thravixa (Emergent Biosolutions,USA), which targets the *Bacillus anthracis* toxin, reducing the ability of the bacterium to cause disease.[11] Studies in rabbits, and phase 1 clinical trials indicate that the antibody is well-tolerated and decreases mortality rates in the animal model. Further identification of novel, highly-conserved bacterial targets for antibody therapy is required to render these technologies a viable therapeutic option.

Antimicrobial peptides (AMPs) (60 in AntibioticDB)

AMPs are naturally-occurring peptides, often present in the innate immune system, that demonstrate antibacterial activity, and are evolutionarily conserved with a diverse range of functions. They are not only effective as antibiotics but also demonstrate activity against fungi and viruses.[12] Most AMPs act against bacteria via membrane permeabilisation, which is possible due to the AMP's amphipathic structure, allowing them to bind to, and penetrate, bacterial membranes. Unfortunately, most AMPs have toxicity issues, hampering their development into therapeutic drugs.[13] One of the main problems with AMPs derived from human immune effectors is the risk that bacteria may become resistant thus making the immune system redundant. Creating semi-synthetic AMPs using prediction models can help reduce toxicity and improve efficacy[14] as well as generate variation in the AMP structure. However, due to poor pharmacokinetics of many AMPs, they have been limited to exploration as topical applications.[15] Of the 60 listed, research into 23 is no longer active. Thirty-seven products are in active pre-clinical development including agents with activity against both Gram-negative and Gram-positive bacteria. AA-139 (Arenicin), developed by Adenium Biotech, Denmark, is currently in pre-clinical development and shows activity against a variety of Gram-negative bacteria including *Escherichia coli, K. pneumoniae, P. aeruginosa* and *A. baumannii.* NAI-603, developed by NAICONS, Italy and NAI-107 developed by Sentinella Pharmaceuticals, Inc. (previously owned by NAICONS), are both currently in pre-clinical development for MRSA. Two AMPs, Lytixar (LTX-109 by Lytix Biopharma, Norway) and Pexiganan by Dipexium Pharmaceuticals (DPRX) are currently in phase 2 and 3, respectively, for topical administration.

Defensins are a cationic subgroup of AMPs which play a crucial role in innate bacterial immunity.[16] Due to the defensin's cationic (positive) charge they can bind to negatively-charged bacterial

membranes, producing pore-like structures and enhancing permeability. Brilacidin (Cellceutix, USA), a defensin-mimetic compound is currently in clinical trials for a wide-range of non-infective clinical indications including ulcerative colitis and mucositis in addition to phase 2 clinical trials of acute bacterial skin and skin structure infections (ABSSSI), results of which demonstrated non-inferiority to daptomycin.[17] Celluceutix is investigating Bilacidin and similar compounds pre-clinically for the management of Gram-negative and fungal infections.

Bacteriocins are AMPs produced by bacteria to defend against competing prokaryotes. Academia has primarily focused on the lantibiotics, which facilitate their action by inhibiting cell wall biosynthesis leading to membrane instability and cell death.[18] Therapeutic use has been hampered by their narrow spectrum, expense of production and limited tissue distribution. AntibioticDB contains examples of several compounds that could serve as a scaffold for optimisation and development into therapeutic drugs. For example, Asahikasei Pharma Corp., Japan was developing API7444 for the treatment of MRSA and penicillin-resistant *Streptococcus pneumoniae*. While this compound showed potent activity *in vitro*, its activity against MRSA in mouse models was markedly lower than that of existing treatments and so the compound was discontinued in 2004.[19]

Bacteriophage endolysins (15 plus four bacteriophage delivery systems in AntibioticDB)

Endolysins (or lysins) are hydrolytic enzymes produced by bacteriophages that target the peptidoglycan layer of bacteria triggering lysis. Several potential candidate compounds such as CF-301 has completed phase 1 (ContraFect, USA). This compound is under development for the treatment of resistant *S. aureus* bloodstream infections. Phico Therapeutics have developed a novel bacteriophage engineered to deliver a DNA-binding protein with cidal antibacterial action. Their first product to enter clinical trials is SASPject™ PT1.2, studied in the treatment of *S. aureus*-related infections. Phico have further products in pre-clinical studies for the treatment and management of *Pseudomonas, Klebsiella* and *E. coli* infections. Fifteen further compounds are listed in pre-clinical development with activity mainly against Gram-positive bacteria. The only exception is PlyF307 (Laboratory of Bacterial Pathogenesis and Immunology, The Rockefeller

University, New York, New York, USA) that demonstrated activity against *A. baumannii* biofilms both *in vitro* and *in vivo.*[20]

Endolysins are ineffective against Gram-negative bacteria since their outer membrane prevents access to the peptidoglycan wall.[21] A novel approach to circumvent this problem is to combine endolysins with an antimicrobial peptide in order to breach the outer membrane. One example is Art-175 (Laboratory of Gene Technology, KU Leuven, Belgium), which combines an endolysin with a targeting peptide that transports the endolysin through the outer membrane of Gram-negative bacteria. Art-175 demonstrated potent activity against *P. aeruginosa,*[22] suggesting potential in the development of future therapies.

In addition to the use of therapeutic phage lysins, whole bacteriophage therapy has long been considered a potential treatment for antimicrobial-resistant infections. While this has gained traction in some parts of the world, further development is required, especially with the potential for bacteria to develop phage resistance.[23]

Beta-lactam antibiotics (220 in AntibioticDB)

Beta-lactams are a broad class, all containing the characteristic four-membered lactam ring, and include: carbapenems, cephalosporins, monobactams and penicillins. Their action is facilitated through interaction with penicillin-binding proteins (PBPs), enzymes involved in peptidoglycan and cell wall biosynthesis, causing cell lysis through weakening of the peptidoglycan layer. The foremost resistance determinant for this class of drugs is deactivation by bacterial beta-lactamases.

There are 47 carbapenems listed; four are under active investigation, two are in pre-clinical studies and two are in clinical trials. In pre-clinical investigations FSI-1671 and FSI-1686 (Achillon/FOB Synthesis) have demonstrated efficacy against Gram-negative bacterial infections.[24] Imipenem with relebactam (MK-7655) (Merck, USA) is a carbapenem/beta-lactamase inhibitor combination that is currently moving into phase 3 clinical trials for the management of hospital-acquired and ventilator-acquired pneumonia and against imipenem resistant infections. In 2016, a phase 3 study of the meropenem-vaborbactam (another carbapenem-beta-lactamase inhibitor) combination

product (Medicines Company, USA) in complicated UTIs was carried out. In February 2017, a New Drug Application (NDA) was filed with the FDA.

Of the 98 cephalosporins listed in AntibioticDB only four remain in active development. Cephalosporins are semi-synthetic agents based on the natural product produced by *Cephalosporium acremonium*. Two of the four cephalosporins listed are currently in pre-clinical development. The fate of one of these products is however unsure; CB-027 a cephalosporin was in the Cubist Pharmaceuticals programme and had demonstrated broad-spectrum activity against several drug-resistant strains including MRSA, *P. aeruginosa* and *K. pneumoniae.*[25] Following the takeover of Cubist by Merck no evidence can be found that development of this product is continuing. Two further cephalosporin-containing products cefiderocol (a siderophore cephalosporin) and the combination ceftaroline/avibactam are currently in phase 3. Currently there is only one licensed monobactam in clinical use, aztreonam. A combination product of aztreonam/avibactam is currently in active development in phase 2.

Two hundred and three beta-lactams (including combination products) have been identified which are no longer the focus of active research and development. These include 43 carbapenems, 98 cephalosporins, 15 monobactams and 14 penicillins.

Efflux inhibitors (13 in AntibioticDB)

Efflux pumps are trans-membrane proteins that can extrude diverse substrates, and constitute one of the most common mechanisms underlying intrinsic drug resistance;[26] inhibiting their activity increases bacterial susceptibility to the compounds extruded. MBX 2319 (Microbiotix Inc, USA) a pyranopiridine compound in pre-clinical studies inhibits the action of the *E. coli* AcrB multi-drug resistance efflux pump. AcrB can extrude a wide array of antibiotics including chloramphenicol, fluoroquinolones and beta-lactams. Use of inhibitors should restore activity to these drugs. Optimisation of the molecular scaffolds of these inhibitors for enhanced efficacy and species specificity is under active research.

Development has stopped for the eleven remaining compounds. One, MC-04124, was only discontinued following the closure of Essential Therapeutics, who were developing several efflux inhibitors. Molecules such as these may make good candidates for continued development.

Fab inhibitors (Twelve in AntibioticDB)

Bacterial fatty acid synthesis (FAS-II) is maintained by a series of mono-functional enzymes that make up the FAS-II pathway. FabI or Enoyl–ACP reductase, is a key enzyme in the final steps and is conserved throughout most bacterial species. There are eight FabI inhibitors undergoing investigation, with four currently in clinical trials.[27-29] Debio1450, Debio1452 (Group, Switzerland) and CG-400549 (CrystalGenomics, South Korea) are currently in phase two and being developed for the treatment of acute bacterial skin and skin structure infections. FAB001/MUT056399 (Fab Pharmaceuticals, India) is a narrow-spectrum FabI inhibitor being developed against MRSA.[27] The four FabI inhibitors currently in pre-clinical development are mostly aimed at Gram-positive bacterial infections with the exception of PT52 and PT68 (Diphenyl ethers) (Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, Colorado, USA), which has demonstrated activity against the Gram-negative bacteria *Burkholderia pseudomallei.*[30]

FtsZ inhibitors/cell division inhibitors (Two in AntibioticDB)

FtsZ is the earliest protein involved in bacterial cytokinesis, its closest homologue in eukaryotic cells is tubulin; there is interest in utilising FtsZ and other crucial proteins in the bacterial cell division pathway as potential targets.[31] AntibioticDB contains two FtsZ inhibitors, TXA-709 and PC190723, both in pre-clinical development with Taxis Pharmaceuticals incorporated.

Glycopeptides (including lipoglycopeptides) *(29 in AntibioticDB)*

Glycopeptides are glycosylated non-ribosomal peptides, comprising both natural and semi-synthetic products, showing activity against Gram-positive bacteria. They bind to a fragment of the outer peptidoglycan layer, D-alanyl-D-alanine, causing inhibition of transglycosylation and transpeptidation, disrupting cell wall synthesis and leading to cell lysis and death. Due to poor permeability and active efflux, glycopeptides have limited activity against Gram-negative bacteria. We include lipoglycopeptides, which are semisynthetic compounds produced through the addition of a lipophilic side chain to the glycopeptide base. Currently there is one agent in pre-clinical development, three in clinical development. In addition, telavancin, dalbavancin and oritavancin have recently received marketing approval. Ramoplanin (Nanotherapeutics, USA) and TD-1607 are currently in phase two and one, respectively. TD-1607, a glycopeptide-cephalosporin hybrid, is

297 being tested in the management of acute bacterial skin and skin structure infections and
298 ramoplanin is being tested for the treatment of *Clostridium difficile.*[32]

299 Development of 23 glycopeptides in AntibioticDB has been discontinued. Following the takeover
300 of Wyeth by Pfizer AC98-6556, their 'cell wall synthesis inhibitor' research programme was
301 discontinued in 2009.

302 *Lincosamides (three in AntibioticDB)*

303 Lincosamides inhibit protein synthesis by affecting the assembly of the 30S ribosomal complex.[33]
304 AntibioticDB contains three lincomycin analogues and derivatives, with very little academic pursuit
305 beyond discovery. Most of these compounds had adverse toxicological effects in humans,
306 although these were not directly cited as the reason for discontinuing research. Examples include
307 rancomycin 1 and 2,[34] which showed potent broad-spectrum activity, but were discontinued at the
308 preclinical stage due to toxicity.

309 *Lipopeptides (Seven in AntibioticDB)*

310 With discovery of daptomycin (1986), lipopeptides represent the latest antibiotic class to be
311 approved. They consist of linear or cyclic peptides with a fatty acid group covalently linked to the
312 N-terminus. It is thought that they bind to the bacterial cytoplasmic membrane and aggregate.
313 One lipopeptide, surotomycin (Cubist), was in phase 3, testing its use against *C. difficile*-
314 associated diarrhoea; however, the programme stopped following acquisition of Cubist by Merck.

315 *LptD/Imp inhibitor (one in AntibioticDB)*

316 Murepavadin (POL7080 Polyphor, Switzerland) is currently in phase two. It is a protein epitope
317 mimetic LptD inhibitor being developed for the treatment of *P. aeruginosa* ventilator-associated
318 bacterial pneumonia, lower respiratory tract infections and bronchiectasis.[35]

319 *Macrolides and Macrocycles (59 in AntibioticDB)*

320 These agents are based on naturally-occurring polyketides, produced by bacteria such as
321 *Micromonospora*.[36] The macrolide ring gives the compounds their antibacterial functionality and
322 allows reversible binding to the 50s ribosomal subunit. Three macrolides are currently under
323 active investigation. Solithromycin (Cempra Inc.) has completed phase three for community-

acquired pneumonia,[37] however its 'new drug application' to the Food and Drugs Administration (FDA) in the US was rejected in December 2016. Before a re-application can be made the FDA requested further clinical safety information and assurances on the manufacturing facility. A second macrolide, nafithromycin (Wockhardt) will shortly be entering phase 2 for the treatment and management of community-acquired pneumonia. RBx 14255 (Department of Infectious Diseases, New Drug Discovery Research, Ranbaxy Research Laboratories, R & D, Gurgaon, India) is currently in pre-clinical development for the treatment of infection by macrolide-resistant *Streptococcus pneumoniae.*

Fifty-six macrolides in AntibioticDB were discontinued (24 categorised as ketolides and four azolides) many due to adverse toxic effects in humans or inferior activity to similar, already marketed compounds. Several macrolides were also discontinued due to poor stability *in vivo*. One example is difficidin (Merck & Co., USA), which, despite showing broad-spectrum activity against aerobic and anaerobic bacteria, was unstable at differing pHs and easily oxidised. This drug showed little activity in a mouse model when administered subcutaneously, but was highly effective when administered through intraperitoneal injection, suggesting that metabolism prevented it from reaching the infection site.

Moenomycins (One in AntibioticDB)

Moenomycins act through direct inhibition of peptidoglycan glycosyltransferases, which are crucial in the last stages of bacterial cell wall synthesis. Research into therapeutic use has been limited due to suboptimal pharmacokinetics, but they represent an attractive scaffold for antibiotic discovery and development. They have recently been shown to be active against multi-drug resistant *Helicobacter pylori.*[38]

Nanoparticles (Three in AntibioticDB)

Nanoparticles are between 0.1 and 100 nm; their small volume to surface area ratio gives them unique properties that can be manipulated to target specific bacterial components via novel mechanisms. In 2011 IBM developed 'ninja particles', which were biodegradable nanoparticles that could target MRSA, and act through a similar mechanism as some immune effectors. These

ninja particles target the membrane and cause instability, resulting in lysis. There was also a low propensity to select for resistance.[39]

It is well-documented that metal alloys have antibacterial properties,[40] and two nanoparticles derived from heavy metals are in pre-clinical development for the treatment of infectious disease, including both silver (nano-Ag) and gold (nano-Au) nanoparticles. Nano-Ag's antimicrobial action is mediated by its binding to the bacterial cell membrane causing dissipation of proton motive force and membrane instability.[41] Gold nanoparticles appear to have a more diverse mechanism of action; they have been shown to inhibit the tRNA-binding ribosomal subunit and also to inhibit the action of ATP synthase, having a deleterious effect on bacterial metabolism.[42] Gold nanoparticles have also been shown to increase chemotaxis and have subsequent potential to be used in drug-delivery systems.[43] An issue with nanoparticles can be their efficacy in the presence of serum, as serum-protein interactions dissipate nanoparticle activity. Gnanadhas *et al.*[44] have demonstrated that by citrate-capping silver nanoparticles, their interaction with serum proteins could be reduced. This reduction also correlated with a higher cell uptake of free nanoparticles, thereby increasing efficacy and antibacterial activity.

Nitrofurans (two in AntibioticDB)

Nitrofurantoin and furazolidone are currently the only nitrofurans licensed for therapeutic use. Recent studies have shown that nitrofurantoin may be a candidate for revival in the treatment of ESBL-producing *E. coli* lower UTIs,[45] implying that nitrofurans may be a good base for future redevelopment for treatment of susceptible organisms resistant to first line antibiotics. One example from AntibioticDB is AS17665, which was discontinued by Abbott Laboratories in 1962. While the exact reason for discontinuation is unclear, the antibiotic was shown to be primarily active against tumours, and hence toxicity is a possible concern. Despite this, the compound was shown to be active against *S. aureus*, *Streptococcus pyogenes, E. coli* and *Salmonella* Typhimurium.

Oxazolidinones (80 in AntibioticDB)

Oxazolidinones (e.g. linezolid) display antibacterial activity against Gram-positive bacteria, but have poor anti-Gram-negative efficacy. Their mechanism is via inhibition of protein synthesis

through binding to the P-site of the ribosomal 50S subunit. Currently, four out of the six active oxazolidone compounds listed in the AntibioticDB are in clinical development. MRX-II (MicuRx Pharmaceuticals, USA) is one of two listed oxazolidinones in pre-clinical development,[46, 47] however any information concerning its development has not been updated since 2012, possibly indicating that it has been dropped for further research. Three oxazolidones currently in clinical trials including MRX-I (MicuRx Pharmacueticals, USA) in phase 3 studies for the treatment of skin and soft tissue infections. The remaining two compounds, radezolid and LCB01 0371, are in phase 2. Radezolid (Melinta Therapeutics, USA) has demonstrated activity against Gram-negative infections and only for *Haemophilus influenzae*.[48] Whilst LCB01 0371 (LegoChem Biosciences, South Korea) is under investigation for the treatment of Gram-positive infections.

Development of 74 oxazolidinones in AntibioticDB has ceased. One, PNU100592 (Pharmacia Corp., USA) was being developed for the treatment of MRSA. This molecule was discontinued due to its inferior activity when compared with linezolid. Many other oxazolidinones were discontinued due to high levels of toxicity. Utilisation of this molecular scaffold to reduce toxicity may represent an avenue for the development of novel protein synthesis inhibitors with reduced propensity to select for resistance. Interestingly, when combined with quinolones, the combination includes Gram-negative bacteria in the spectrum of activity.[49]

Pleuromutilins (Ten in AntibioticDB)

Pleuromutilins inhibit the 50S ribosomal subunit; retapamulin, was approved for human use in 2007,[50] but, it has been difficult to develop compounds for systemic use,[50] mainly due to difficult peptide chemistry. Nabriva Therapuetics, Austria, has five candidate compounds in research and development with one, lefamulin (BC 3781), progressed to phase 3. Lefamulin is under development for the treatment of acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia.[51, 52]

Polymyxins (Two in AntibioticDB and one polymyxin analogue)

Polymyxins are produced by non-ribosomal peptide synthetases in Gram-positive soil bacteria such as *Paenibacillus polymyxa*.[53] They have selective activity against Gram-negative bacteria,

targeting the lipid A component of the outer membrane.[54] Currently, the only polymyxin in clinical use is polymyxin E (colistin), but, due to high incidence of nephrotoxicity,[55] colistin is administered as an agent of last resort against infections by multi-drug resistant bacteria, such as *A. baumannii.* The two polymyxins in pre-clinical development and listed in AntibioticDB are NAB-739 and CA-824, which are being developed by Northern Antibiotics (Finland) and Cantab Anti-infectives, respectively.

Quinolones, Fluoroquinolones and Other Topoisomerase Inhibitors (146 in AntibioticDB)

The targets for topoisomerase inhibitors in bacteria are DNA gyrase and DNA topoisomerase IV, which are enzymes that regulate bacterial DNA supercoiling and relaxation.[56] There are currently five fluoroquinolones in AntibioticDB undergoing active research and development, four are in clinical studies. Following two successful phase 3 studies, known as PROCEED, a 'new drug authorisation' for delafloxacin (Melinta Therapeutics, USA and Abbott) was submitted in October 2016 for the treatment of gonococcal, skin and soft tissue infections. Zabofloxacin (Dong Wha Pharmaceuticals, South Korea) is in phase 3 for the treatment of community-acquired bacterial pneumonia and quinolone-non-susceptible gonorrhoea. Finafloxacin (MerLion Pharmaceuticals, Germany) has been licensed topically for the treatment of *otitis externa*. An oral formulation continues through phase 2 clinical studies for the management of urinary tract, intra-abdominal and, skin and soft tissue infections. Nemonoxacin (TaiGen Biotechnology Co., Taiwan) a non-fluorinated quinolone is currently in phase 3[57] and has promising broad-spectrum activity targeting a variety of infections including vancomycin-non-susceptible MRSA.

There are 114 discontinued quinolones and fluoroquinolones documented in AntibioticDB. Research and development into many of these agents was discontinued due to toxicity, although some agents were discontinued due to financial constraints. MCB 3382, a fluoroquinolone–oxalidinone hybrid, was in development by Morphachem AG before the company merged with Biovertis AG, leading to the discontinuation of their antibacterial research programme.

Sideromycins and sidophore antibiotics (eight in AntibioticDB)

Siderophores are iron chelators, which can be exploited in a number of therapeutic processes.[58] Sideromycins are antibiotic moieties covalently linked to siderophores, allowing for their selective uptake into the bacterium via the native iron transport systems.[59] This feature is useful in the context of Gram-negative bacteria whereby the outer membrane forms a barrier to drug entry, and the concentration of some antibiotics required for entry into the cell can become toxic to humans. One such example is cefiderocol a siderophore cephalosporin, which forms a chelation complex in the presence of iron. Cefiderocol (Shionogi, Japan) has recently completed phase 3 for multi-drug resistant Gram-negative infections.

HKI 9924109 (Basilea Pharmaceutica AG, Switzerland) is an ampicillin adduct linked to a synthetic siderophore. This compound was discontinued at the preclinical stage due to its inability, even at high concentrations, to inhibit the growth of non-fermenting Gram-negative bacteria.[60] Despite the shortcomings of some siderophore-antibiotic conjugates, they remain a useful tool for targeted therapeutics.[61] For example, Wencewikz *et al*[62] have reported a siderophore-carbacephalosporin conjugate that selectively targets *A. baumannii.*

Streptogramins (Five in AntibioticDB)

Streptogramins are produced by several *Streptomyces* species and are structurally unique, having similar mechanisms of action to macrolides and lincosamides, therefore cross resistance is possible by target modification thus limiting therapeutic use.[63] Examples are pristinamycin 1 and 2, which are produced by *Streptomyces pristinaespiralis*. There are no streptogramins in active research and development listed in AntibioticDB.

Streptothricins (one in AntibioticDB)

Streptothricins have broad-spectrum activity against bacteria and fungi;[64] their therapeutic potential has been hampered by toxicity problems, but they have been successfully utilised for the treatment of infectious diseases in crop plants; streptothricin-type antibiotics have been marketed as fungicidal agents in China.[65] One streptothricin compound in AntibioticDB is LL-AB 664, which was reported in 1967.[66] New streptothricin class antibiotics have been isolated and assessed for their antimicrobial potential recently, some of these display potent activity against a variety of bacteria, particularly *Mycobacterium tuberculosis.*[67, 68] If the problem of resistance to these

compounds and toxicity in humans can be overcome, then they may represent a new avenue for antibiotic development. There are no streptothricins in active research and development listed in AntibioticDB.

Sulphonamides (Two in AntibioticDB)

Sulphonamides are synthetic compounds based on the industrial dye sulfachrysoidine;[69] they are analogues of p-aminobenzoic acid (PABA) and inhibit folic acid biosynthesis via competitive inhibition of the enzyme dihydropteroate synthetase.[70, 71] This competitive inhibition is bacteriostatic, disrupting DNA synthesis and bacterial growth. ABEPI 1 and 2 are currently in pre-clinical development.[72] Some antibiotics can act as efflux inhibitors and ABEPI 1 and 2 have been shown to inhibit the efflux activity of the nosocomial bacteria *A. baumannii*, which allows for increased accumulation of the antibiotic minocycline, and subsequent susceptibility to the drug.

Tetracyclines (10 in AntibioticDB)

Tetracyclines are broad-spectrum cyclic antibiotics classified into two types: tetracyclines that bind to the amino-acyl-tRNA acceptor site of the mRNA ribosomal complex, causing disruption of protein synthesis, and those that demonstrate antibacterial activity via cytotoxic perturbation of the cytoplasmic membrane.[73] Out of the four tetracyclines in active development listed in AntibioticDB, two are in pre-clinical development, both by Tetraphase Pharmaceuticals, USA, and two are in phase 3. The two phase three compounds are omadacycline and eravacycline. Eravacycline (Tetraphase Pharmaceuticals, USA) has received mixed results from the phase 3 studies 'IGNITE'. In IGNITE1, eravacycline demonstrated non-inferiority to ertapenem in the management of complicated intra-abdominal infections. In IGNITE2, eravacycline showed inferiority to levofloxacin in the treatment of complicated UTIs.[74]

The IGNITE2 study protocol authorised intravenous to oral switch and further data analysis has suggested participants receiving solely eravacycline intravenously had a more favourable outcome. As a consequence, there is a suggestion that poor clinical outcomes were observed due to problems with the oral eravacycline formulations rather than with the parent compound; two further phase 3 studies (IGNITE3 and IGNITE4) indicated non-inferiority to meropenem in patients with polymicrobial infections. These were included in the recent NDA application.

Omadacycline is a semi-synthetic tetracycline being developed by Paratek Pharmaceuticals, technically classed as a novel aminomethylcycline, the first in its class.[75] The newer tetracyclines appear to avoid active efflux by bacteria and are effective against typical tetracycline-resistant bacteria. The mechanism underlying this phenomenon is unknown.[75] AntibioticDB contains four cyclic tetracyclines that have been discontinued for development as antibacterials.

Miscellaneous molecules (121 in AntibioticDB)

A multitude of molecules that do not fit into pre-defined classes of compounds and inhibiting various bacterial functions have been reported to display antibiotic activity. The differences of the structures of these compounds and the commonly used therapeutic classes may provide avenues to identify novel molecular scaffolds, less prone to degradation by bacterial-resistance determinants. While this may not be an option in cases where resistance has been acquired by target modification, this remains a resource to bring novelty to the antibiotic research pipeline. Some agents may fit within a class but were not described as such when first reported.

Reasons for discontinuing compounds

Few compounds in the development pipeline become drug candidates and even fewer are approved for clinical use. From analysis of the discontinued compounds, most were discontinued in pre-clinical research (Figure 1). This is as expected due in part to the large numbers of analogues that are often discarded for inferior activity. There are many factors to be considered before submission of an IND application relating to a promising drug candidate. These include: *in vitro* and *in vivo* activity (compounds should have non-inferior activity to other compounds and existing drugs), levels of toxicity, pharmacokinetic profile (e.g. bioavailability, half-life), cross-resistance to other antibiotics or resistance development and commercial reasons. In reality, few agents reach the stage where all these data are available, as discovery of a key impeding factor, e.g. high toxicity, may preclude any further research and development. The cited reasons for discontinuation of a particular drug given in AntibioticDB are depicted in Figure 2. As a result of the lack of further pursuit when a compound's poor potential is identified, very few reasons for discontinuation have been published.

Thirty-eight compounds are listed in AntibioticDB where evidence for discontinuation of research was identified as 'due to commercial reasons', company acquisition, or the 'financial circumstances of the developing company'. Examples include: the Genaera 'Magainin program' (company shut down), Essential Therapeutics (bankruptcy) and the Cubist pipeline (acquired by MSD). In these cases, the rights to company assets can be purchased. However, for many early stage compounds, there may not have been a sufficient incentive for these compounds to be purchased. Therefore, it is possible that certain compounds were overlooked, or in too early a stage of development, and that these have the potential to be taken to market without optimisation or be used as intermediates for further analysis and development.

In the last 15 years many large pharmaceutical companies (including Astra-Zeneca, Bristol Myers Squibb, Eli Lilly and Wyeth) discontinued antibiotic research because their pipelines had no viable compounds and/or because of economic factors. To identify novel compounds, European and American researchers and companies turned to target-based discovery to identify agents with novel modes of action, whilst Japan tended towards finding derivatives of existing, successful compounds such as fluoroquinolones and β-lactams. In using target-based discovery, researchers encountered many issues with entry of the antibiotics into bacterial cells. The timeline for antibiotic discovery is illustrated in Figure 3.

Of those agents with a documented reason for termination of development, approximately 50% were discontinued due to toxicity. Many compounds were also discarded where research revealed resistance, unfavourable pharmacokinetics or poor potency. Interestingly, following investigation beyond the published literature from the developer, some compounds were discontinued for "circumstantial reasons", suggesting that this was not due to unfavourable properties of the compound. One example of this is the compound JNJ-17155437, a ketolide antibiotic reported by Johnson and Johnson. Research and development into this compound was discontinued around about the time that questions were raised around another ketolide antibiotic being developed by the company called telethromycin (Ketek). This drug was approved by the FDA and said to be one of the first compounds of its type to circumvent antimicrobial resistance.[76] In the year following initial approval, several deaths were reported due to liver failure in people treated from community-

545 acquired pneumonia with telethromycin. The suboptimal safety profile of this drug and the
546 structurally related JNJ-17155437 may have been the reason for discontinuation of the compound.

Discussion

AntibioticDB was assembled with the intention of generating a platform to facilitate researchers from academic or industry backgrounds to potentially research and develop previously discontinued compounds into new antibacterial drugs. Additionally, it is an accessible source of information to determine the progress of compounds currently in development. While there are databases and publications[5, 77-79] describing the properties of compounds and their status, including the Springer-AdisInsight and Thomson Reuter databases, these are not widely accessible and some are only available on a paid subscription basis. Furthermore, AntibioticDB includes antibacterial compounds no longer in active development, and indicates, where possible, the reasons why development was discontinued. To identify the latter, the published literature, company websites and other databases were interrogated, and individuals with extensive knowledge interviewed. It should be noted that for many of the compounds, there is little available information as they were discontinued in early pre-clinical development and there was no publicly available information.

Several discontinued antibiotic classes and compounds have been revisited to investigate whether there is any merit in developing them for medical use. For instance, in the 1980s daptomycin (LY 146032) was under development by Eli Lilly and Co.; however, in clinical trials, muscle-skeletal damage was shown, and so development of the compound was discontinued. In 1997, Cubist Pharmaceuticals acquired the rights to this drug and after changing the dosing to IV administration once daily, daptomycin was found to be safe. It was approved by the FDA and marketed in 2003.[80] Secondly, pleuromutilins such as tiamulin have been previously used in veterinary medicine, but there is now the prospect of developing them as therapies for humans. GSK developed retapamulin (Altabax) and currently Nabriva is developing a further three compounds,[81] including lefamulin, which is a candidate for treatment of community-acquired pneumonia. A third drug candidate is iclaprim. In 2009, FDA rejected Arpida's application on the grounds of incomplete data to demonstrate efficacy. In April 2015, the FDA accepted the proposal of two further phase 3 trials by Motif Bio who gained the rights to the drug and plan to continue its development.[82] These examples indicate that there can be merit in reinvestigating discontinued

antibiotics for future development, and AntibioticDB will provide a platform to facilitate this. There is a possibility that with the progression of synthetic chemistry and other areas of science, cross-disciplinary approaches may be able to optimise some old compounds to remove unfavourable characteristics and make them more useful in future.[83] For these agents to be developed there will need to be a financial incentive.

There is also the need to consider the target patient of new antibiotics. Some compounds were discontinued due to toxicity, however certain compounds e.g. colistin, despite presenting toxicity issues could progress further through the drug development pipeline. However, with the understanding of AMR, it is probable that many new antibiotics will not be widely used. Many will be kept as reserve agents for compassionate designation usage, i.e. usage in mitigating circumstances, where few other therapeutic options are available; this means that the regulatory authorities may allow companies to provide experimental drugs to people outside of clinical trials. Whilst re-investigating discontinued compounds is a possibility, there are some complications. For instance, the expertise in synthesising certain compounds or their documentation may no longer be available. This is likely for those companies that have ceased their research in this area or become bankrupt. In these cases, many derivatives may have been synthesised from a promising parental compound which demonstrated toxicity or other unfavourable properties. If the information about these derivatives has been lost, reinvestment is high risk, which highlights the importance of an open-access approach to pre-clinical and clinical development of therapeutic drugs. Another complication is that some discontinued compounds may not have been patented as a drug but as an intermediate. If the patent is still valid, another organisation synthesising derivatives, may infringe the patent. Finally, a company investigating old compounds will, to receive regulatory approval, ultimately need to be able to ensure a steady supply of drug.

While the cases of daptomycin and the pleuromutilins show that ‘reviving’ old antibiotics is possible and can be successful, it must be considered whether this is a viable path of antibiotic research and development for other discontinued compounds. It is important to note that the currently prevalent bacteria have evolved and disseminated because of selection by antibiotics in current clinical use. Therefore, further development of old and/or compounds of the same class may not

603 be productive as resistance mechanisms active against these agents may already be widely
604 disseminated. Many of the discontinued compounds in AntibioticDB will not have been tested
605 against current clinical isolates, suggesting a potential difference in efficacy from when they were
606 first screened. Nonetheless, compounds that demonstrate a novel mode of action may evade
607 current resistance issues and thus could be clinically useful. This was the case for daptomycin
608 and the pleuromutilins.

609 The UK AMR Review has questioned the sustainability of the current R&D pipeline for antibiotic
610 development[2] and indicated that for a sustainable future of antibiotic development 15 new
611 antibacterials need to be developed every 10 years. The AMR review also noted that novelty is a
612 direct issue for today's antibiotic development, with no new antibiotic drug classes being developed
613 in the past 30 years (since the lipopeptide daptomycin in 1986). Currently there are 152 active
614 pre-clinical compounds listed in the AntibioticDB. The attrition rate in drug development is well
615 known and based on data provided by the Review on AMR on success rates it is possible that
616 three may be approved for human use by 2025.[2] This demonstrates a possible gap of 12
617 licensable compounds over 10 years. Data from the Review on AMR suggests the number of pre-
618 clinical compounds that require testing in order to generate 15 licensed medicines is approximately
619 590, a shortfall of 440 compounds (Figure 4).

620 Academia has an important part to play in the fight against antimicrobial-resistant infections, with
621 the need for innovation in the field and subsequent development of antibiotics with novel
622 mechanisms of action at its greatest. This alone however is not enough, and only with
623 collaboration between academia, SMEs, big pharma, funding bodies, and governments can this
624 goal be achieved. AntibioticDB, described herein provides a valuable tool for anyone involved with
625 antibiotic discovery, research and development. By providing a history of compounds that have
626 been discontinued with the current status of antibiotic discovery, research and development
627 (including pre-clinical development), AntibioticDB will enable academia and industry alike to
628 explore previously discontinued antibiotics for the treatment of the drug-resistant infections we are
629 faced with today. AntibioticDB is an interactive database; therefore, we call upon all involved in

630 this field be it pharmaceutical companies, university groups or individuals, to help to continue to
631 populate AntibioticDB.

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Author contributions

LJVP conceived and designed the project and wrote the manuscript. LJF reviewed source material and entered information into the database, generated Figure 4 and contributed text for the manuscript. RL reviewed source material and entered information into the database, generated Figure 3 and contributed text for the manuscript. JW reviewed source material and entered information into the database, generated Figures 1 and 2 and contributed text for the manuscript. AJ checked all entries in the database were correct as of March 2017. AM supervised RL, generated the references and contributed to the writing of the manuscript.

Financial interests

None of the authors have any competing financial interests.

Transparency declarations

None to declare.

Legends to Figures

Figure 1. The stages at which antibiotic compounds in this database were discontinued for development (values from AntibioticDB 31st March 2017). As a disproportionate number of compounds are discontinued at the pre-clinical stage, the y-axis is split to reflect this. I: phase one clinical trials; II: phase two clinical trials; III: phase three clinical trials; IV: phase four clinical trials.

Figure 2. The reasons identified for termination of compound development (values from AntibioticDB 31st March 2017). Unknown; Toxicity, either in animals or humans; Inferior: studies showed inferiority to comparator compound. That may have been a marketed or study compound; Resistance, resistance acquired to compound within studies; Commercial, includes bankruptcy, mergers, closing R&D facilities; Clinical results, unfavourable outcomes; Pharmacokinetics, unsuitable parameters; Pharmacodynamics, unsuitable parameters.

Figure 3. A timeline of the discovery of the major classes of antibiotics. From 1986 to 2017, regulatory authorities have approved no new class of antibiotics; this has been termed the 'discovery void'.[84]

Figure 4. Antibiotic discovery, research and developmental pipeline (values from AntibioticDB 31st March 2017). The X-axis represents the average time in years in takes to progress a compound through each clinical stage, with the final stage, Post-marketing surveillance, taking an undetermined amount of time. The percentage between each clinical stage states on average how many compounds will make it to the next stage of clinical development is based on the data provided in the Review on Antimicrobial Resistance.[2]

684 **Table 1: Phases of drug development**

Phase	Comment
1	Typically consist of a small group (20-100) studies in healthy volunteers in a controlled setting to test the compound's pharmacokinetics, toxicity and pharmacology; goal is to determine the maximum tolerated dose range that can be safely used; typically 33% of drugs in phase 1 proceed to phase 2.
2	Expand patient numbers to a few hundred; used to understand the compound's dosing requirements, efficacy and adverse effects; typically 59% continue to phase 3
3	Large, randomised, controlled, multicentre studies in which treatment by the study compound is usually compared against the currently accepted 'gold standard'; success in phase 3 is much higher than in earlier phases, typically ~76%; mostly due to the stringency of previous trials. Phase 3 provides clinical data necessary to file for a new drug application (NDA) potential marketing authorization applicant (MAA); application is usually submitted when there is sufficient data on the safety/pharmacology of the compound; typically ~80% of antimicrobial compounds awaiting approval are granted an NDA
4	Often termed as post-marketing surveillance; the compound is formulated as a medicine and been given full marketing approval; data is usually collected on the safety profile of the drug. Further research can be initiated to test the drug profile in different disease states, for combination therapies, alternative delivery systems and different subject groups if the company chooses to do so. Medicines can be discontinued or withdrawn at this stage if it becomes apparent that the medicine has intolerable adverse effects or is unsuitable for clinical practice

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687 **Table 2: AntibioticDB terms**

Term	Definition
1. Drug name	Current generic name of the compound; alternate or past names are indicated in brackets
2. Drug class	Antibiotics can be classified in two ways: (1) by chemical structure e.g. a fluoroquinolone, and (2) based on the mechanism or target of the compound e.g. a topoisomerase inhibitor; in AntibioticDB, compounds are classified by both methods where applicable
3. Development phase	The highest development phase a compound has reached as of 30 March 2017, for example pre-clinical, phase 1, 2, 3, 4, or marketed
4. Organisation	Represents the party or individual that has been listed as the lead discoverer or developer of the compound; encompasses large pharmaceutical companies, university groups or individuals.
5. Gram-negative activity	Indicates a compound with activity against Gram-negative bacteria which is/was in the process of being developed to target these bacteria; includes compounds with a broad spectrum but are targeted to these bacteria during their development
6. Gram-positive activity	Indicates a compound with activity against Gram-positive bacteria which is/was in the process of being developed to target these bacteria
7. Combination agents	Indicates agents used in combination with other antibiotics or other compounds that enhance antibiotic efficacy of the compound in question
8. Low propensity	Criteria for selection of compounds with 'propensity to select resistant mutants' was only applied if data were available showing that bacteria had been exposed to the compound for the purpose of detecting bacterial resistance, or if resistance had been observed during clinical trial; where no data was available, this parameter was left blank in the database
9. Mechanism of action	The site/s of interaction of the compound with the bacterium e.g. cell wall inhibitor, DNA gyrase inhibitor
10. Target bacteria	If a compound has a broad spectrum of activity, comparative details of its efficacy against Gram-positive and Gram-negative organisms are provided
11. Current status	Gives information on the compound drug: active research (A) or inactive (I)
12. Reason antibiotic not developed	Indicates why a compound failed to advance further or was retracted from market. To gather this information, the Springer database 'AdisInsight' was used; Dr Lynn L. Silver, Dr Jared A. Silverman, Dr Ursula Theuretzbacher and Dr Glenn Tillotson provided additional information. Blank fields in this section indicate that the original author, or authors of subsequent pieces of work, has given no reason as to why a compound may have been dropped, which was often found to be the case for compounds predating 1990
13. Citation	Indicates the journal article/conference abstract that the compound was first described; provided as a web address and/or reference. If more than one source is cited brackets containing the number refers to the reference from which the information was derived. Where possible the first reference will be the first description of the drug (e.g. ICAAC abstract) and the second will be a publication that gives the broadest overview and/or most information regarding the compound

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Bracketed compounds in AntibioticDB represent the most promising compounds discussed of a series of analogues. Information on the inferior derivative compounds can often be found in the reference provided.

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